

COMMUNICATIONS FROM THE DEPARTMENT OF ANATOMY
UNIVERSITY OF LUND, SWEDEN
No 9. 1971

SYMPATHETIC INFLUENCE
ON
INTRACRANIAL PRESSURE

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From the Neurosurgical Clinic A, University Hospital of Lund
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To my family and my parents

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The present dissertation is based on the following papers:

1. Edvinsson, L., Ch. Owman, E. Rosengren and K.A. West (1971). Concentration of noradrenaline in pial vessels, choroid plexus and iris during two weeks after sympathetic ganglionectomy or decentralization. *Acta physiol. scand.* In press.
2. Edvinsson, L., K.C. Nielsen, Ch. Owman and K.A. West (1971). Alterations in intracranial pressure, blood-brain barrier, and brain edema after sub-chronic implantation of a cannula into the brain of conscious animals. *Acta physiol. scand.* In press.
3. Edvinsson, L., Ch. Owman, E. Rosengren and K.A. West (1971). Brain concentration of dopamine, noradrenaline, 5-hydroxytryptamine, and homovanillic acid during intracranial hypertension following traumatic brain injury in rabbit. *Acta neurol. scand.* In press.
4. Edvinsson, L. and K.A. West (1971). The time-course of intracranial hypertension as recorded in conscious rabbits after treatment with different amounts of intracisternally injected kaolin. *Acta neurol. scand.* In press.
5. Edvinsson, L. and K.A. West (1971). Relation between intracranial pressure and ventricular size at various stages of experimental hydrocephalus. *Acta neurol. scand.* In press.
6. Owman, Ch., E. Rosengren and K.A. West (1971). Influence of various intracranial pressure levels on the concentration of certain arylethylamines in rabbit brain. *Experientia.* In press.

7. Edvinsson, L., Ch. Owman and K.A. West (1971). Changes in continuously recorded intracranial pressure of conscious rabbits at different time-periods after superior cervical sympathectomy. *Acta physiol. scand.* In press.
8. Edvinsson, L., Ch. Owman and K.A. West (1971). Changes in cerebral blood volume of mice at various time-periods after superior cervical sympathectomy. *Acta physiol. scand.* In press.
9. West, K.A. (1971). Influence of superior cervical sympathectomy on traumatically induced brain edema. *Acta path. microbiol. scand.* In press.
10. Edvinsson, L., Ch. Owman and K.A. West (1971). Modification of kaolin-induced intracranial hypertension at various time-periods after superior cervical sympathectomy in rabbits. *Acta physiol. scand.* In press.
11. Edvinsson, L., Ch. Owman and K.A. West (1971). Sympathetic influence on cerebral blood volume: Time-dependent effect of decentralisation of the superior cervical ganglia in mice. *Experientia.* In press.
12. Edvinsson, L., Ch. Owman and K.A. West (1971). Intracranial pressure in conscious rabbits after decentralization of the superior cervical sympathetic ganglia. *Acta physiol. scand.* In press.

They will be referred to in the text as Paper 1, Paper 2 etc.

I. INTRODUCTION

Intracranial pressure (in the present study measured as VFP) and its variations are of central importance in clinical neurology and neurosurgery. The CBV and the CSF circulation are the primary factors involved in the regulatory mechanism of intracranial pressure. There is much evidence that, within a wide range of changes in cerebral perfusion pressure (the difference between arterial blood pressure and intracranial pressure), the brain is capable of maintaining a constant blood flow through intrinsic regulation phenomena involving arterial $p\text{CO}_2$ and extracellular fluid pH (see Ingvar et al. 1968, Luyendijk 1968, Zwetnow 1970a). However, it has recently been demonstrated that adrenergic sympathetic nerves innervate intracranial vessels as well as the choroid plexuses (Nielsen and Owman 1967, Edvinsson et al. 1971a; see further below) suggesting a sympathetic influence on CBV and CSF dynamics - i.e. on intracranial pressure.

It has since long been known that stimulation of the cervical sympathetic trunk usually produces a clearly notable constriction of the pial arteries and a slight reduction in the cerebral blood flow (Forbes and Wolff 1928, Ask-Upmark 1935, Boukaert and Jourdan 1936, 1949, Forbes and Cobb 1939, Lubsen 1941, Schneider 1953, Browne et al. 1955, Holmqvist et al. 1957, Ingvar 1958, Kunc

Abbreviations used:	ACh = acetylcholine
	CBV = cerebral blood volume
	CSF = cerebrospinal fluid
	DA = dopamine
	HVA = homovanillic acid
	5-HT = 5-hydroxytryptamine
	NA = noradrenaline
	VFP = ventricular fluid pressure

1958, Bloor et al. 1969, James et al. 1969, Kobayashi et al. 1971). Observations concerning the cerebrovascular effects of cervical sympathectomy or blockade of the cervical sympathetic trunk are contradictory: some authors have reported signs of cerebral vasodilation while others have seen no significant effects (Talbot et al. 1929, Leriche and Fontaine 1936, Forbes and Cobb 1938, Harmel et al. 1949, Naffziger and Adams 1950, Shenkin et al. 1950, 1951, Murakami and Ando 1955, James et al. 1969). This had led to the widely held view that the sympathetic nervous system is of little or no importance in the regulation of the cerebrovascular bed (and hence in influencing the intracranial pressure).

The autonomic innervation of the pial arterial system includes both parasympathetic and sympathetic nerves (Forbes and Wolff 1928, Cobb and Finesinger 1932, Chorobski and Penfield 1932, Rosenblum 1965, Hagen and Wittkowski 1969, Nelson and Rennels 1970, Nielsen et al. 1971a). The adrenergic sympathetic nerves enclose the pial and superficial cortical arteries down to a diameter of 15–20 μ (Falck et al. 1965, Nielsen and Owman 1967, Spoendlin and Lichtensteiger 1967, Donáth 1968, Falck et al. 1968, Ohgushi 1968, Kajikawa 1968, 1969). Arterial branches radiating into the outer layers of the cortex are supplied only by few adrenergic fibers, and in the deeper regions of the brain the arteries are usually devoid of adrenergic innervation (Falck et al. 1965, Donáth 1968). The pial veins receive only a scarce adrenergic nerve supply (Nielsen and Owman 1967). The adrenergic fibers innervating the pial circulation arise in cell bodies located in the superior cervical sympathetic ganglia (Falck et al. 1965, Nielsen and Owman 1967, Ohgushi 1968, Kajikawa 1968, 1969). As shown by electron microscopy the terminal portion of the perivascular sympathetic nerves ends at a distance of 780–1000 Å from the vascular smooth muscle cell (Hagen and Wittkowski 1969, Nelson and Rennels 1970, Nielsen et al. 1971a). Although the distance across which a neurotransmitter substance might diffuse and cause excitation of smooth muscle cells is unknown it is evident that the morphological substrate exists for a true pial adrenergic innervation.

The choroid plexuses, an important site for CSF formation have been shown to receive an adrenergic nerve supply in several species including man using the

fluorescence histochemical method of Falck and Hillarp (Edvinsson et al. 1971a). The adrenergic nerve fibers, arising in the superior cervical sympathetic ganglia, were observed to run mainly along arterial vessels but were also present in between the vessels and the plexus epithelial cells. The choroid plexus in the lateral and third ventricles received more nerves than the plexus in the fourth ventricle. Evidence based on denervation studies has recently been obtained indicating a sympathetic influence on carbonic anhydrase activity (and thus probably on CSF formation) in the choroid plexus (Edvinsson et al. 1971b).

The present series of experiments is concerned with the following questions:

- (1) How is the noradrenaline concentration in intracranial sympathetic nerves affected by pre- and postganglionic denervation?
- (2) What effect does these operation procedures have on VFP in conscious rabbits?
- (3) Does the denervation influence the brain edema induced by the trauma during the pressure recording?
- (4) How does kaolin-induced intracranial hypertension affect VFP after sympathetic denervation?
- (5) What is the relation between VFP and ventricular size as well as brain amine concentrations?
- (6) Is it possible that changes in VFP after pre- and postganglionic sympathetic denervation are related to alterations in CBV?

II MATERIAL AND EXPERIMENTAL DESIGN

Animals. All experiments were performed on albinotic and randomly pigmented rabbits of either sex weighing 2-3 kg and on albinotic mice weighing 25-30 g. During the recording experiments the conscious rabbits were maintained sitting in an iron-mesh box with the head and neck free. All animals were fed freely with their standard food during the entire experimental period.

Pressure cannula. The intracranial pressure, measured as the VFP, was recorded

in conscious rabbits via a cannula inserted into the left lateral ventricle of the brain. The cannula (Fig. 1a) was devised according to the particular requirements in the present series of experiments (see Owman and West 1970). The part of the cannula resting in the brain measured 7 mm in length and 1.3 mm in diameter, thus occupying 0.0093 cm^3 volume. The outlet of the cannula was connected via a pressure-sensing polyethylen catheter to a Statham Model P23AC transducer, the entire system being filled with physiological saline. The pressure recordings (Papers 2, 4, 5, 6, 7, 10 and 12) were performed on a Grass Model 7 Polygraph.

VFP recording and calculations. After shaving the convexity of the animal's head, a 3-4 cm long skin incision was made in the midline over the frontoparietal region under local anesthesia (2-3 ml of 2% lidocain; Xylocain, Astra, Sweden). A burr hole (3.2 mm in diameter) was placed with its center 1.5 mm rostral to the coronar suture and 3 mm to the left of the sagittal suture. The cannula, connected to the polygraph, was filled with physiological saline and, with its orifice near the tip closed, was inserted through the burr hole towards the left lateral ventricle. Correct position of the cannula was checked by recording the presence of characteristic deflections produced by the arterial pulsations (Fig. 1 b). The burr hole was tightly sealed by the rubber plug around the basal part of the cannula (Fig. 1 a). If respiratory and arterial deflections were not directly obtained, the animal was discarded in order to avoid further traumatization of the brain during the manipulation. A horizontal plane between the skull surface at the burr hole and the longitudinal central axis of the horizontally placed pressure transducer was used as zero reference plane (for further details, see Owman and West 1970).

Pressure calculations were performed according to the principles described in Papers 2 and 7.

Surgical experiments. The following special procedures were performed: intracisternal kaolin injections (Papers 4, 5, 6 and 10), extirpation of the superior cervical sympathetic ganglia (postganglionic denervation) of cranial structures including the cerebrovascular bed (Papers 1, 7, 8, 9 and 10), preganglionic denervation (decentralization) of the superior cervical ganglia (Papers 1, 11 and 12),

intravenous injections of ^{131}I -labelled albumin (Papers 8 and 11), intravenous infusion (Paper 2) and intraventricular injection of trypan blue (Paper 4).

Fluorescence microscopy of amines. The distribution of adrenergic nerve fibers was investigated by fluorescence microscopy of noradrenaline according to the method of Falck and Hillarp (Falck 1962, Falck et al. 1962, Corrodi and Hillarp 1963, 1964, Falck and Owman 1965, Corrodi and Jonsson 1967).

Chemical determinations of amines. The brain tissue NA and DA were determined fluorometrically (Bertler et al. 1958, Häggendal 1963). 5-HT determinations were performed according to Bertler (1961) and Bogdanski et al. (1956), and HVA by the method described by Andén et al. (1963).

Statistical calculations. The Student's t -test was used in statistical calculations of differences between mean values (Bonnier-Tedin 1957).

III. EVALUATION OF METHODS

As a basis for studies of sympathetic influence on VFP certain problems associated with the methodology had to be evaluated.

Postdenervation NA concentration in pial vessels, choroid plexus and iris

(Paper 1)

The detailed pattern of changes in the concentration of NA transmitter in rabbit pial vessels and choroid plexus during the first 2 weeks after excision or decentralization of the superior cervical sympathetic ganglia was determined fluorometrically. The noradrenaline content in iris, which is a well studied model organ, was used for comparison (Paper 1). It was found that the pial vascular preparation contained $1.50 \mu\text{g/g}$ NA, the choroid plexuses $0.40 \mu\text{g/g}$ and iris $4.32 \mu\text{g/g}$. After bilateral superior cervical ganglionectomy (postganglionic denervation) the NA was significantly reduced at 18 hrs, and at 48 hrs it had disappeared from all tissues. This absence of NA in the tissues persisted during the remainder of the experimental period.

After preganglionic denervation of the ganglia (decentralization) little or

no change was noted in the NA concentration of the pial vascular preparation during the initial postoperative days. After 1 and 2 weeks, however, the content had increased by 40 and 20%, respectively. In the choroid plexus the level of NA was significantly reduced (by about 50%) 12 hrs after decentralization, and it was still reduced by approximately 25% compared with untreated controls after 48 hrs. During the remainder of the experimental period the level was not significantly lower than that in the controls. In the iris the NA level remained essentially unchanged during the entire decentralization period.

The functional aspects of these postoperative variations in the level of tissue NA with regard to CBV and VFP will be discussed in Chapter IV.

Effect of pressure cannula on VFP and brain monoamines

(Papers 2 and 3)

The direct pressure recording used introduces a traumatic factor which increases VFP with associated effects on brain monoamines. After implantation of the pressure cannula, the initial VFP (in non-denervated rabbits) was about 15 mm physiological saline but increased rapidly during the first 6 hrs after the implantation to approximately 5 times the initial value. The pressure slowly normalized (Paper 2) but was still 50 hrs after insertion of the cannula about twice as high as initially. The pressure increase was shown to be accompanied by a transient blood-brain barrier damage and by a brain edema. The brain edema persisted during the experimental period but showed maximal histological extension at about 20 hrs after initiation of the pressure recording (i.e. when the VFP was maximum).

According to the classical Monro-Kellie doctrine, it could be expected that the increased VFP should be compensated more rapidly than presently observed. Since, however, this compensatory mechanism requires intact CSF dynamics it is suggested that some impairment in CSF absorption has been produced, e.g. in the cannulated area not far from the superior sagittal sinus. It is also possible that the continuously and slowly developing traumatic edema has counter-balanced the normal defence mechanisms according to which the pressure will

not start to decrease until the edema subsides (i.e. after about 25 hrs). The findings thus represent methodological artefacts which have to be taken into consideration when interpreting pressure curves after such recordings in sympathectomized animals.

Since brain monoamines are located in neurons (cf. Andén et al. 1966) it was assumed that registration of quantitative changes in the monoamine levels during various pressure conditions would be a good means of evaluating the neuronal involvement. The above-mentioned intracranial hypertension was shown (Paper 3) to be associated with a progressive and statistically significant decrease from 0.59 $\mu\text{g/g}$ to 0.48 $\mu\text{g/g}$ in the concentration of brain DA. Brain HVA, the main metabolite of DA, showed a tendency to lower values (about 0.35 $\mu\text{g/g}$) than in the control animals (0.41 $\mu\text{g/g}$ tissue) during the 48 hrs period with the pressure cannula, whereas brain NA was transiently increased at 16 hrs to 0.34 $\mu\text{g/g}$ from the normal level of 0.27 $\mu\text{g/g}$. The brain stem concentration of 5-HT was 0.28 $\mu\text{g/g}$ in the untreated control animals and did not change significantly during the experimental period.

The variations in the concentrations of brain DA, HVA and NA in relation to different VFP levels indicate a certain degree of neuronal involvement in the brain parenchyma at the levels of VFP recorded. The different reaction of the DA and NA neuron systems was assumed to relate to the topographical position of these neuron systems with regard to the ventricular system: DA neurons are situated close to the ventricular system mainly in the neostriatum whereas the NA neurons are more diffusely dispersed in the brain (Andén et al. 1966). Thus, it is possible that the intracranial pressure forces which are prominent at the borderline of the ventricles have induced more pronounced damage to DA nerve fibers, whereas NA-containing neuron systems are only slightly and transiently disturbed. This would agree with the findings that the concentration of 5-HT in the brain stem - more remote from the ventricular system - exhibited almost no variation during different VFP levels. However, it seems not very likely that these variations in the concentrations of brain monoamines exert an influence on the course of VFP per se

(West and Roos 1970). Conceivably they are associated with disturbances in the oxidative metabolism known to occur in the brain during intracranial hypertension (Siesjö and Zwetnow 1970, Zwetnow 1970b).

Kaolin-induced intracranial hypertension related to ventricular
size and brain monoamines

(Papers 4, 5 and 6)

Intracisternal injection of kaolin suspension is known to produce impairment of CSF circulation resulting in intracranial hypertension and hydrocephalus (Dixon and Heller 1932, Granholm 1966). The impairment is considered to be a result of a diffuse inflammatory meningeal response and subarachnoid fibrosis as observed in chronic experiments on cats and dogs (Schurr 1953, Griffith and Roberts 1938, Hochwald et al. 1969). In Paper 4 it was shown that the VFP measured 2 days after an intracisternal injection of 0.5 ml of a 30 g % sterilized suspension of kaolin (hydrated aluminium silicate in 0.9% physiological saline) resulted in an increase in VFP by about 55 mm physiological saline compared to untreated controls. Injection of trypan blue through the VFP cannula revealed a total kaolin blockade of the outlets from the fourth ventricle in most of the animals. If kaolin was located more remote from the foramina of the fourth ventricle, inconsistent pressure elevations were observed. Thus kaolin is not an entirely reliable drug for producing hydrocephalus in rabbits. It has, however, certain advantages: intracisternal injection of kaolin can be performed with ease, without operative interference with the cranial bone structures and without extensive damage to the dura and the subarachnoid space. Different amounts of the kaolin suspension (0.5 or 0.65 ml) did not significantly change the level of the initial VFP or the course of the VFP patterns when recorded continuously during 2 days in the conscious rabbits (Paper 4). At the end of the 2-day recording period the VFP showed a tendency to a decrease compared to the initially measured VFP. This observation was assumed to reflect alterations in CSF circulation shown to occur in man and animals during intracranial hypertension in the form of reduced rate

of CSF formation, increase in the rate of CSF absorption or development of new absorption pathways (Bering and Sato 1963, Langfitt et al. 1965, Calhoun et al. 1967, Hochwald et al. 1969, Sahar et al. 1969a and b, Sahar et al. 1970a and b, Lorenzo et al. 1970, Milhorat et al. 1970).

In Paper 5 it was shown that a high VFP developed within the first 2 days after kaolin-administration after which the pressure decreased and reached almost normal values during the remainder of the observation period (1 month). In spite of this decrease in VFP, the lateral ventricles of the brain remained enlarged. This stage of hydrocephalus is thus probably equivalent to the compensated or normal pressure hydrocephalus described in man (Foltz and Ward 1956, Adams et al. 1965, Hakim and Adams 1965, Geschwind 1968 and others).

Intracranial hypertension induced by intracisternal injections of kaolin were shown to be accompanied by alterations in the levels of cerebral monoamines (Paper 6). Thus, the concentrations of NA and 5-HT in the brain were significantly reduced as measured 2 days after the kaolin injection. Then a normalization occurred within a week. The brain DA level, however, showed a progressive decrease during the entire experimental period. In the brain stem the 5-HT level was not significantly changed, whereas the NA level transiently decreased at 2 days after the treatment. The amine changes in brain and brain stem could be directly correlated to the VFP levels: changes were most pronounced when pressure was high. It is notable that the amine reaction occurs simultaneously with the disturbance in oxidative metabolism in brain tissue during high intracranial pressure (Siesjö and Zvetnow 1970, Zvetnow 1970b), indicating a common casual mechanism or, the reactions may even be associated with each other. The progressive reduction in the brain DA level seems to be indicative of a neuronal damage and may - as assumed in Paper 3 - be due the topography of the DA terminals, which are mainly present in the neostriatum bordering the lateral ventricles. This is consistent with the findings that the structural damage during hydrocephalic conditions affects the periventricular structures more than areas away from the ventricles (Hochwald et al. 1969, Clark and Milhorat 1970, Weller

et al. 1970). The sustained fall in the DA concentration was assumed to contribute to the explanation of those extrapyramidal symptoms, such as tremor, ataxia, imbalance and clumsiness frequently observed in hydrocephalic animals (Paper 4) and hydrocephalic children (Hagberg and Sjögren 1966). There is no evidence, on the other hand, that changes in the levels of brain monoamines, seen e.g. in patients with Parkinson's disease (West and Roos 1970), have any overt influence on intracranial pressure.

IV. EVALUATION OF RESULTS

The previous Chapter III has been concerned with an evaluation of certain methodological problems associated with the planned studies on the sympathetic influence on intracranial pressure. On the basis of these methodological prerequisites, a series of experiments have been performed to study the effect of operative interference with the cranial sympathetics on VFP. These experimental results will be evaluated in this following Chapter IV

Postganglionic denervation and VFP

(Papers 7, 8, 9 and 10)

The first series of experiments were concerned with the course of changes in VFP recorded during 2 days in animals subjected to bilateral removal of the superior cervical sympathetic ganglia at different time-periods before the recordings (Paper 7). It was found that the VFP varied greatly depending on the amount of time that had elapsed between the operation and the beginning of VFP recording. The VFP was lowered compared to that in untreated controls during the 2-day recording period which was started 5-8 hrs after the ganglionectomy. Four days after the postganglionic denervation, the VFP was markedly increased compared to controls during the entire 2-day pressure recording period. At fourteen days after sympathectomy the VFP showed during the major part of the recording

period normal or even subnormal values when compared to the pressure levels in non-sympathectomized control animals. The variation in VFP at various periods after superior cervical ganglionectomy must reflect changes in some intracranial mechanism that receives a sympathetic innervation and which influences the intracranial pressure. The possibility that the intracranial vessels (and thus CBV) forms part of this mechanism has been tested.

The decline of the NA transmitter content in brain perivascular sympathetic nerves was found to start within about 18 hrs after bilateral excision of the superior cervical sympathetic ganglia (Paper 1). Two days postoperatively the main pial arteries were devoid of their NA. This condition persisted during the remainder of the 2-week experimental period. In order to evaluate the vasomotor effect of this NA leakage and subsequent disappearance from the main pial arteries a series of experiments were performed to study CBV in mice at different time-periods after postganglionic denervation (Paper 8). The relative blood volume of the mouse brain (ratio between plasma volume of the brain and plasma volume of a reference tissue not denervated by cervical sympathectomy - small intestine) was estimated by measuring the radioactivity in the two tissues after intravenous injections of ^{131}I -labelled serum albumin (RISA), which does not penetrate the blood-brain barrier (Bakay and Lee 1965, Risberg et al. 1969). In order to get precise information about the volume of the vascular bed in a given organ at a given moment after the operation, the animals were killed by direct immersion into liquid nitrogen after a suitable mixing time following injection of the albumin (Friedman 1955). The relative volume of the brain vascular bed can be estimated without correction for the amount of activity injected or decay if a reference tissue is chosen that has a similar blood volume as the brain but is not innervated from the superior cervical sympathetic ganglia. The small intestine fulfilled these requirements (Everett et al. 1956, Alm et al. 1971). By this technique, no change in the CBV was noted 6 hrs after sympathectomy. However, 12 hrs postoperatively, when the NA leakage was shown to occur from the degenerating perivascular sympathetic nerves (Paper 1), the relative

blood volume was reduced by 28%, thus indicating a vasoconstriction at this postoperative stage. One day after sympathectomy the relative blood volume in brain was then almost doubled, to 34% above that of the non-sympathectomized controls, probably a result of vasodilation. The blood volume then returned to control values within a further 3 days postoperatively and showed at 14 days subnormal values when compared to unoperated controls.

Assuming that the sympathetic nerves to the brain vessels are vasoconstrictor, these alterations are well explained by changes in the adrenergic transmitter and receptors known to occur after denervation. The NA content in sympathetically innervated organs has been found to remain virtually unaltered during the first 8 hrs following sympathectomy (Paper 1, Weiner et al. 1962, Malmfors and Sachs 1965, Sears and Gillis 1967, Sedvall 1969). Subsequently, a leakage of the stored transmitter occurs from the degenerating sympathetic nerve terminals (Paper 1, Weiner et al. 1962, Benmiloud and Euler 1963, Malmfors and Sachs 1965, Van Orden et al. 1967, Sedvall 1969) and this has been shown to result in an activation of the effector structures (Sears and Bárány 1960, Coats and Emmelin 1962, Langer 1966, Emmelin and Ohlin 1969, Lundberg 1969). This activation of the smooth muscles in the brain vessels agreed with a vasoconstriction 12 hrs after sympathectomy. The receptor activation during degeneration of the severed sympathetic nerves continues for about 12 hrs (Emmelin and Ohlin 1969, Lundberg 1969) after which the smooth muscles relax. Such a relaxation of the brain vascular smooth muscles when noradrenaline has disappeared from the degenerating nerves (Paper 1) after sympathectomy was reflected by the increase in the CBV at 24 hrs postoperatively (Paper 8).

It has been shown (Langer et al. 1967) in studies on the denervated feline nictitating membrane that the adrenergic receptors becomes sensitized to catecholamines by more than 100 times at 2 days and almost 1000 times at 2 weeks after denervation. In agreement with this, the volume of the brain vascular bed had returned to its original volume at 4 days and to even subnormal volume 14 days after sympathectomy probably because of a progressive increase in

vascular tone due to a developing supersensitivity in the denervated vascular smooth muscles to existing circulating catecholamines.

The studies on the pattern of changes in CBV after postganglionic sympathetic denervation are in good agreement with the observed alterations in VFP after the denervation, and it is thus possible that the VFP variation is a consequence of the changes in blood volume. However, it could be expected that the altered CBV should be compensated more rapidly with subsequent normalization of VFP. It can therefore be assumed that the direct recording method involves an impairment of the CSF circulation as previously discussed (on p. 11). Thus, the recording technique used has the great advantage that the sympathetic influence on VFP becomes well measurable due to impairment of normally operating compensatory mechanisms. Since also the choroid plexuses receive aadrenergic innervation (Edvinsson et al. 1971a) it is, of course, not unlikely that the denervation has directly effected CSF formation. It is conceivable that a reduced plexus blood flow will reduce CSF formation and contribute to the low VFP shortly after and 2 weeks after ganglionectomy (cf. Paper 7), whereas an increased blood flow will enhance CSF production and add to the hypertension 1 week postoperatively (cf. Paper 7). This is in agreement with the observation that rabbit plexus carbonic anhydrase activity significantly increased a week after sympathetic denervation (Edvinsson et al. 1971b). It can be expected that the presence of any secretory sympathetic nerves in the choroid plexus should counteract the vascular changes in this tissue with regard to CSF formation.

It was demonstrated in Paper 2 that implantation of the pressure cannula was followed by a period of intracranial hypertension, probably on the basis of a local traumatic edema combined with impairment of CSF absorption due to the injury of the brain in the region of the cannula. This increment in VFP formed a methodological artefact which was corrected for in the sympathectomy - VFP studies. However, during the course of the study the possibility appeared that this artefact was not itself constant: the amount of traumatic edema might

vary with the changes in CBV after denervation (it is unlikely that sympathectomy should have any pronounced effect on the impaired CSF resorption).

Paper 9 describes experiments in which the amount of increase in brain water content (referred to as brain edema) due to thermic trephine traumatization was studied at various times after superior cervical sympathectomy.

The time-related alterations in the CBV after postganglionic denervation was in Paper 9 shown to reflect changes in the amount of traumatically induced brain edema. Thus, the amount of traumatic brain edema was reduced by about 50% 32 hrs after sympathectomy in the traumatized telencephalon compared to traumatized but not sympathectomized control animals. At 5 days after sympathectomy the amount of traumatic brain edema was equal in denervated and non-denervated animals, whereas at 15 days after sympathectomy the traumatically induced edema was about 50% higher than in the control animals.

The experiments show (Paper 9) that the amount of traumatic brain edema is changed by sympathectomy, that the changes are not directly correlated to the changes in VFP, but that they may have a certain quantitative influence on the VFP curves presented not only in Paper 7 but also in Paper 10.

Thus, shortly after sympathectomy the low VFP is associated with a comparatively low brain edema, at 1 week postoperatively the VFP is high although the edema is as in non-sympathectomized animals, whereas at 2 weeks when the VFP is again low, the denervation has promoted an increase in the edema.

Principally the same sequence of pressure changes as those reported in Paper 7 at various time-periods after sympathectomy were observed also in kaolin-treated animals, although the pressure levels were markedly exaggerated (Paper 10). Kaolin treatment in these experiments was used as a tool to "sensitize" the recording system by further minimizing normal pressure-defence mechanisms through a more pronounced impairment of CSF absorption. Under these conditions, relatively small changes in intracranial volume (inter-

preted as changes in CBV) will result in relatively pronounced alterations in VFP (Langfitt et al. 1965a and b, Langfitt 1968). It can then be expected that any compensation of an intracranial hypertension is accomplished by an increased CSF absorption via normal pathways not involved in the kaolin blockade (Bering and Sato 1963, Sahar et al. 1969a), via the formation of alternate pathways for its absorption (Sahar et al. 1969a and b, 1970a and b) and/or a reduced CSF formation (Calhoun et al. 1967, Hochwald et al. 1969, Lorenzo et al. 1970). These defence mechanisms were considered to act together with a decrease in CBV during the first days after ganglionectomy (and combined kaolin treatment) thus explaining the low VFP (Paper 10). Although the same defence mechanisms in CSF formation and absorption could be expected to act also 6 days after sympathectomy, the enlargement of the brain vascular bed (Paper 8) was considered to exceed these mechanisms resulting in the observed lethal increase in VFP of the kaolin-treated animals at this post-operative stage. Furthermore, it can not be excluded that the surgical interference with the cervical sympathetic system has added an increased CSF formation (as evidenced by increased carbonic anhydrase activity) a week after denervation (Edvinsson et al. 1971b). The VFP increase observed initially in the kaolin-treated animals subjected to ganglionectomy 2 weeks earlier may be ascribed to a stress-induced vasoconstriction of the supersensitive intracranial vessels (Paper 10) promoting an enlargement of the well developed traumatic brain edema at this stage (Paper 9). When the stress-induced vasoconstriction subsides, and the intracranial hypertension is compensated by the above-mentioned mechanisms, the VFP becomes lowered (Paper 10).

Preganglionic denervation and VFP

(Papers 11 and 12)

In order to evaluate the significance of the central control of the superior cervical sympathetic ganglia with regard to their influence on intracranial pressure, the relative CBV was estimated in mice (Paper 11) and the VFP was

recorded in conscious rabbits (Paper 12) at different times within 2 weeks after preganglionic denervation.

After preganglionic denervation (decentralization) the preganglionic, cholinergic nerve fibers degenerate and lose their ability to synthesize the ACh transmitter within 3 days (MacIntosh 1938, Feldberg 1943). This is associated with an impairment and finally abolishment of synaptic transmission in the sympathetic ganglion (Coppée and Bacq 1938, MacIntosh 1938). Probably due to the lack of physiological stimulation (under conditions of continued NA synthesis in the postsynaptic neuron) after deprivation of the afferent innervation, the NA level increases in the ganglion cells (Giacobini 1970) and in the nerve terminals as seen in the pial vessels (Paper 1). The ACh leakage assumed to occur initially after severing the (preganglionic) nerve fibers has been shown to result in an activation of the effector structure (Emmelin and Strömblad 1957, Emmelin 1968), in our case represented by the postsynaptic neuron. This activation can be expected to result in at least a certain degree of NA release from the postganglionic sympathetic nerves. Such a transmitter release was assumed to be the explanation for the observed tendency to a reduction of CBV 6 hrs after decentralization (Paper 11). Subsequently, when the ACh transmitter has disappeared from the preganglionic nerve terminals (and the activation of the postganglionic neuron subsides), there is a vasodilation and hence an increase in CBV, which was observed to be maximal at 18 hrs postoperatively (Paper 11). Due consideration being taken to the influence of the direct recording technique used on pressure defence mechanisms, these observations on the variations in CBV after decentralization of the superior cervical sympathetic ganglia were considered to explain at least some of the changes in VFP levels noted after this operation (Paper 12). Thus, initially after decentralization of the ganglia the VFP was shown to be transiently and slightly lowered (reduced CBV) compared to untreated control animals. The VFP was then found to be elevated during the majority of the 2-week post-operative observation period (slight but constant increase in CBV).

V. GENERAL SUMMARY AND CONCLUSIONS

The aim of the present investigations has been to find indications for a sympathetic influence on intracranial pressure (measured as ventricular fluid pressure) in rabbits using surgical interference with the cranial sympathetics.

(1) A special cannula was constructed for direct continuous recording of ventricular fluid pressure in conscious rabbits.

(2) A period of intracranial hypertension followed the implantation of the cannula and was considered to be mainly a result of a local traumatic brain edema and impaired cerebrospinal fluid absorption near the cannula. These observations have been utilized for correction of methodological errors.

(3) Two structures involved in the maintenance of the intracranial pressure - intracranial vessels and choroid plexuses - are known to receive a sympathetic nerve supply. Postganglionic denervation results in a fall in the noradrenaline transmitter concentration of these structures within 18 hrs. Noradrenaline has disappeared at 2 days. After preganglionic denervation tissue noradrenaline either slightly increases (pial vessels) or shows a transient reduction followed by a normalization (choroid plexus and iris).

(4) After postganglionic denervation the ventricular fluid pressure is initially lower than in unoperated controls. After about 1 week it is significantly increased, followed by a normalization 2 weeks postoperatively. The same sequence of changes upon postganglionic denervation were seen also after blockade of cerebrospinal fluid absorption by intracisternal kaolin injection but they were exaggerated, probably because of a pronounced impairment of pressure defence mechanisms which "sensitize" the recording situation. After preganglionic denervation, the intracranial pressure was initially reduced, but during most of the remaining 2-week observation period it was

above that in unoperated controls.

(5) Traumatic brain edema (developing e.g. around the implanted pressure cannula) varied after postganglionic denervation; initially it was less pronounced than in non-denervated controls, 1 week postoperatively it had the same size as the controls, whereas at the 2-week stage it was considerably increased.

(6) The intracranial hypertension levels under study were found to reduce chemically measurable brain monoamines, most evident in areas near the ventricular system, less evident in the brain stem. The findings are suggested to relate to the degree of neuronal involvement during intracranial hypertension. In spite of a normalization of the increased ventricular fluid pressure, the (lateral) cerebral ventricles remained enlarged in size during a 1-month observation period.

(7) In studies on mice using the organ radioactivity from systemically injected ^{131}I serum albumin (RISA) as a measure of relative organ blood volume, it has been found that the cerebral blood volume changed according to a pattern very similar to that of the ventricular fluid pressure after pre- and postganglionic denervation.

(8) The presently used direct recording technique, which to a great extent seems to reduce masking compensatory effects by the pressure defence mechanisms, has revealed a sympathetic influence on ventricular fluid pressure. This can be explained by an influence of vasoconstrictor sympathetic nerves on cerebral blood volume, although an associated effect on the cerebrospinal fluid formation from the sympathetically innervated choroid plexuses can not be excluded.

ACKNOWLEDGMENTS

This work was supported by the Association for the Aid of Crippled Children (New York), by grant No. B71-14X-732-05 from the Swedish Medical Research Council, and was carried out within a research organization sponsored by the Swedish Medical Research Council (Projects No. B71-14X-712-06A and B71-14X-56-67A).

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